

## LETTERS

## Leukoencephalopathy with vanishing white matter presenting with presenile dementia

Vanishing white matter disease (VWM, OMIM #306896) is an autosomal recessive leukoencephalopathy typically of childhood onset. Patients usually present with progressive cerebellar ataxia and spasticity. MRI shows a diffuse leukoencephalopathy. Part of the abnormal cerebral white matter has the signal intensity of CSF on all pulse sequences, reflecting progressive disappearance of white matter, which is replaced by fluid. Five disease genes have been identified, *EIF2B1-5*, which encode the five subunits of translation initiation factor eIF2B, essential for translation of mRNA into protein.<sup>1</sup> Adult onset cases have been described.<sup>2-4</sup> The p.Arg113His mutation in *EIF2B5* is the most frequent mutation both in children and adults and is usually associated with a relatively benign phenotype.<sup>2</sup> We report a late onset case homozygous for the p.Arg113His mutation in *EIF2B5*, presenting with slowly progressive cognitive impairment with a neuropsychological profile of subcortical dementia.

## CASE REPORT

A 55-year-old woman was referred to our dementia unit because of inability to perform her work in the past 6 months. She committed errors, forgot her duties and required supervision at work. The family noted a progressive neglect in personal hygiene, reduced variety in cooking, memory deficits and repetitive speech. The basic

activities of daily life were preserved. Neurological examination disclosed generalised hyperreflexia and bilateral Babinski signs, but was otherwise normal. The patient scored 26/30 on the Mini-Mental State Examination (MMSE), with partial disorientation in time and delayed recall failure that improved with cues. Language and praxis were preserved, as well as insight, although she tended to minimise the deficits. No changes in affect or psychotic symptoms were present. Neuropsychological assessment showed a profile of subcortical dementia, with spatial disorientation, cognitive slowing, disturbances in attention, naming deficits, visuoconstructive impairment and frontal lobe deficits. Memory tests revealed a deficit in immediate and delayed memory with relatively preserved recognition; visual memory was also impaired. Cortical functions, such as praxis, visual gnosis and expressive language, were relatively spared. After 4 years of follow-up, she is clinically stable, without functional changes in daily life and at neurological examination; a 6 point decline on MMSE was found as a result of decreased orientation in time and delayed recall.

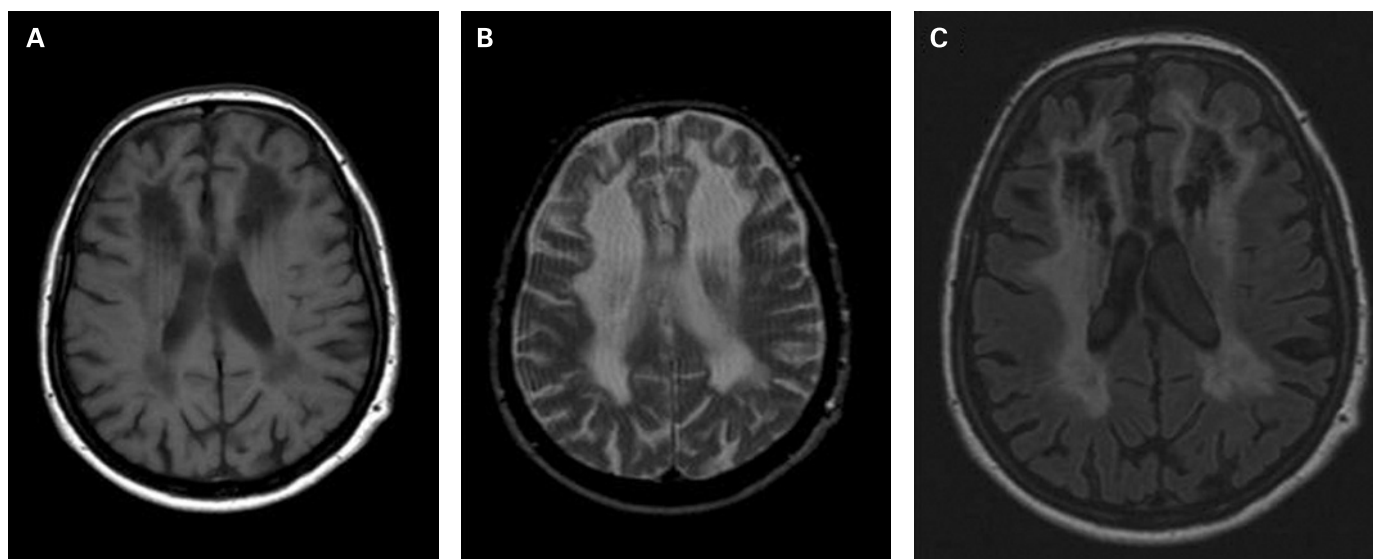
An MRI performed 30 months after onset showed a diffuse leukoencephalopathy with bilateral symmetrical hyperintense confluent areas on T2, PD and fluid attenuated inversion recovery (FLAIR), filled with hypointense areas on T1 and FLAIR similar to cerebrospinal fluid (fig 1), typical of VWM. Laboratory examinations were normal, including blood folate, cobalamin, thyroid function and studies for autoimmune disease. Brain perfusion single photon emission computed tomography (SPECT) with HMPAO was also normal. A second SPECT performed 2 years later revealed a mild bilateral frontoparietal hypoperfusion.

A genetic study was performed, as described previously,<sup>5</sup> which revealed the presence of the homozygous mutation p.Arg113His in *EIF2B5* that confirmed the diagnosis.

## COMMENT

VWM is a rare disorder that usually occurs in children and presents with cerebellar ataxia, spasticity and mild mental impairment.<sup>1</sup> Episodes of rapid deterioration can occur following stress conditions (febrile infections, minor head trauma, fright). Adult onset VWM is rare and may present with different phenotypes than early onset VWM. The initial symptoms may include seizures,<sup>2</sup> psychiatric symptoms,<sup>2,3</sup> dementia<sup>4</sup> or motor deterioration. Episodes of rapid deterioration are less frequent. Some adults with two pathogenic eIF2B mutations do not exhibit any neurological abnormalities.<sup>2</sup> The latest onset of disease has been reported in three patients at ages 40–42 years, one starting with dementia, one with behavioural abnormalities<sup>3,4</sup> and one with cerebellar ataxia. Our patient has the latest known onset of disease, 55 years. Her initial symptom was mental decline without other neurological signs, except for a mild pyramidal syndrome. Disease severity is correlated with age at onset; later onset is generally associated with a more benign disease course. Which subunit is mutated does not impact on the phenotype.

VWM is caused by mutations in either of the five genes encoding the five subunits of the eukaryotic translation initiation factor 2B (eIF2B), most of them affecting the epsilon subunit (*EIF2B5*).<sup>5</sup> At least 148 patients have been reported with mutations and about 100 eIF2B mutations have been identified.<sup>1</sup> The p.Arg113His mutation in *EIF2B5* is the most



**Figure 1** MRI showing severe diffuse leukoencephalopathy with cystic degeneration and a signal similar to cerebrospinal fluid. (A) T1, (B) T2 and (C) fluid attenuated inversion recovery sequences.

frequent mutation<sup>5</sup> and is usually associated with a benign phenotype.<sup>2</sup>

VWM can manifest with a presenile dementia syndrome. The typical MRI alterations, which already occur in presymptomatic stages, usually lead to analysis of the genes *EIF2B1-5*. Demonstration of mutations in either of these genes allows a definitive diagnosis.<sup>1</sup>

**J Gascon-Bayarri,<sup>1</sup> J Campdelacreu,<sup>1</sup> C Sánchez-Castañeda,<sup>1</sup> S Martínez-Yélamos,<sup>1</sup> M Moragas,<sup>1</sup> G C Scheper,<sup>2</sup> M S Van der Knaap,<sup>2</sup> Ramon Reñé<sup>1</sup>**

<sup>1</sup> Unitat de Diagnòstic i Tractament de les Demències, Neurology Service, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; <sup>2</sup> Department of Child Neurology, VU University Medical Centre, Amsterdam, The Netherlands

**Correspondence to:** Dr R Reñé, Unitat de Diagnòstic i Tractament de les Demències, Neurology Service, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Spain; [ramonrenye@hotmail.com](mailto:ramonrenye@hotmail.com)

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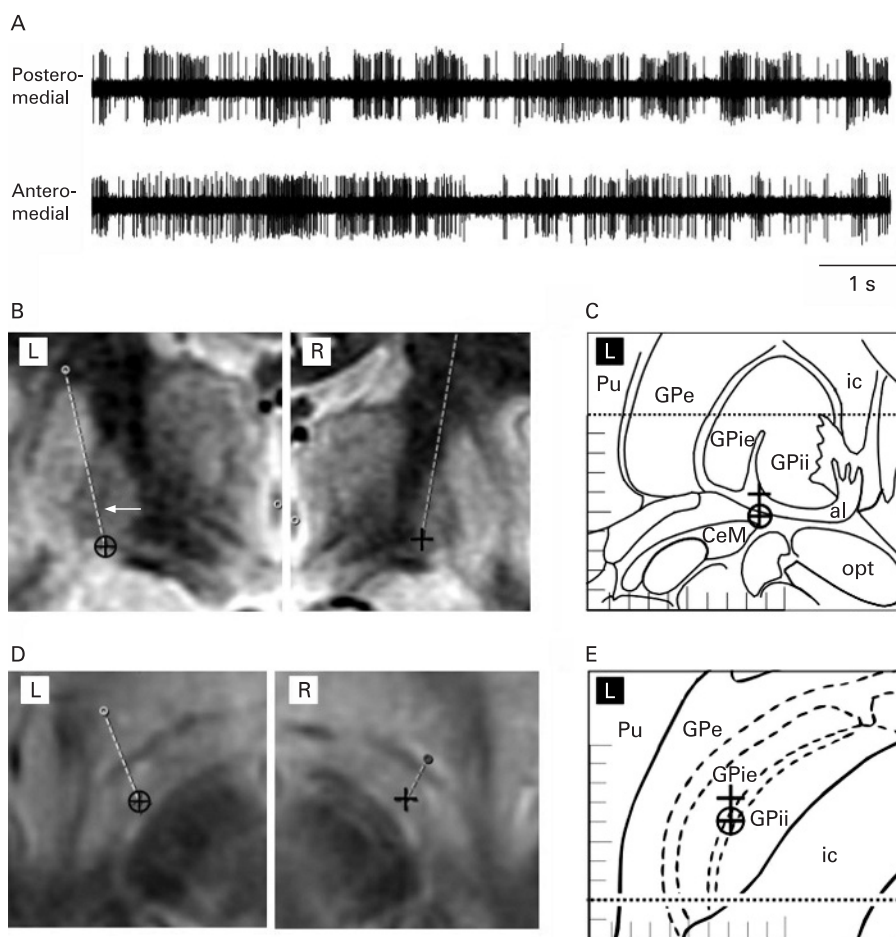
## Successful GPi deep brain stimulation in a patient with adult onset primary axial dystonia

Axial dystonia is a rare manifestation of adult onset primary segmental dystonia. Typically, patients present with cranio-cervical dystonia spreading to the trunk but not to the extremities. Affected patients are disabled predominantly by flexion spasms of the trunk which are worsened on action, especially during standing and walking.<sup>1</sup> Response to drug therapy is often poor and local botulinum toxin injections are of limited value in these patients. Here we report a patient with primary axial dystonia who was successfully treated with bilateral deep brain stimulation (DBS) of the globus pallidus internus (GPi).

## CASE REPORT

This 39-year-old woman presented with a 3 year history of truncal spasms with predominant flexion and lateral bending of the trunk. Onset was subacute over several weeks during her first pregnancy. There was gradual spread of dystonia from the trunk muscles to both shoulders and also to the neck, although axial dystonia remained predominant. Three years after disease onset, action induced dystonia was so severe that she was hardly able to walk because her trunk was flexed by almost 90° and also severely bent to the left side whenever she attempted to walk (see video segment 1 online). She also had right torticollis and left laterocollis. There was no dystonia in the

arms or legs apart from mild writer's cramp. Burke–Fahn–Marsden's Dystonia Motor Score (BFMD) was 22.5. Past medical and family history was unremarkable. MRI of the brain and extensive laboratory investigations were all normal. No mutation in the *DYT1* gene was found. Medical treatment with zolpidem, zopiclone, bromazepam and the combination of trihexyphenidyl and tetrabenazin was ineffective. Also, botulinum toxin injections into the neck muscles did not relieve her symptoms. In view of the symptom severity, we opted for bilateral implantation of DBS electrodes in the GPi given previous and recent favourable reports of GPi stimulation in patients with primary generalised and segmental dystonia.<sup>2,3</sup>



**Figure 1** (A) An example of two simultaneously recorded neurons from two different regions of the left external segment of the internal globus pallidus (GPie) separated by 2 mm. An irregular firing pattern is readily discernible by visual inspection of the raw trace. (B, C) Position of the most distal contact of the quadrupolar DBS electrode reconstructed from a postoperative stereotactic CT scan, superimposed on frontal sections of a T2 weighted MRI of the patient's brain and a corresponding frontal section of the Schaltenbrand–Bailey stereotactic atlas (3.5 mm anterior to the midcommissural point). The white arrow indicates the position of the recording shown in (A). (D, E) MRI based and atlas based (4.5 mm below the anterior commissure–posterior commissure plane) reconstruction of the electrode position in the horizontal plane. On both sides, the most distal contacts are located in the subpallidal fibre field lateral to the optic tract. Note that the reconstructed electrode positions for both sides are superimposed on the same atlas slide for the left hemisphere. al, ansa lenticularis; CeM, central amygdaloid nucleus; GPe, external globus pallidus; GPii, internal segment of the internal globus pallidus; ic, internal capsule; opt, optic tract; Pu, putamen.



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